

Clinical determinants of mental disorders occurring during the infertility treatment

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Summary

Today, infertility is an increasingly common medical and social problem. Treatment of infertility has been revolutionised by the introduction and continuous improvement of assisted reproductive technology (ART). In most countries an increase in the frequency of performing of such procedures is observed. Infertility, mental disorders and infertility treatment are related in a very complex way. Most research indicates that the presence of psychiatric disorders (including depressive disorders which is the most common among them) in patients treated for infertility, can affect the efficacy of gynaecological therapy. According to other studies an ineffective treatment for infertility could be an independent risk factor for the development of psychiatric disorders (particularly psychotic disorders and addiction). Despite the increasing prevalence of assisted reproduction technologies (ART), there are no uniform standards for psychological and psychiatric procedures in the case of mental health complications of the diagnosis and treatment of infertility. The aim of this paper was the analysis of the studies concerning the mental health aspects in the course of the infertility treatment. The studies were analysed in terms of their relevance to clinical practice in the field of psychiatric and psychological support for patients treated for infertility.

Key words: infertility, infertility treatment, mental disorders

Introduction

The World Health Organization (WHO) defines infertility as “the inability to conceive despite regular sexual intercourse held over two years, without the use of any contraceptive methods” [1]. According to WHO estimates from the 1990s, infertility affects 10–18 % of couples of the reproductive age [2]. Over the last thirty years the infertility treatment has been revolutionized by the introduction of assisted reproductive technologies (ART), which are the subject of continuous improvement [3]. In 2003,

more than 400,000 ART cycles were performed around the world [4]. In most countries there has been a steady increase in the frequency of use of such procedures [5]. The most commonly used among them are: intrauterine insemination with husband semen (IUI-husband), intrauterine insemination with donor semen (IUI-D), in vitro fertilization with subsequent transfer of live or frozen embryos (IVF), in vitro fertilization with intracytoplasmic sperm injection (ICSI).

From the Polish analysis of randomly selected 1,705 ART cycles carried out in 2005–2010 in the Department of Reproduction and Gynaecological Endocrinology of Medical University of Białystok suggests that the effectiveness of therapy reflected in pregnancies is about 40% [6]. While in European countries the percentage of children being born as a result of the ART procedures ranges from 0.2 to 4.2% of all births [7].

At the moment it is difficult to estimate the percentage of children in Poland being born, as a result of assisted reproduction procedures. In contrast, recommendations of Polish scientific societies regarding diagnosis and treatment of infertility, which have become the standard in the treatment of this disorder in Poland was published only in 2012 [8].

Infertility, mental disorders and infertility treatment are related in a very complex way. The presence of psychiatric disorders can affect fertility, while the diagnosis of infertility can result in the development of the adjustment disorders or the mental disorders associated with stress. Similar bimodal relations are supposed to characterize the impact of mental disorders (primarily depression and anxiety) and the results of infertility treatment. This also applies to the relationship between the unsuccessful ART procedures and the development of mental disorders in both females and males.

Several years ago, research on the psychological and psychiatric aspects of infertility focused on the analysis of the factors that can lead to infertility (especially in relation to idiopathic infertility). Another line of research has focused on attempts to describe the relationship between the different categories of mental disorders, fertility and infertility.

In a recent work concerning the relationship between mental disorders and infertility published in Polish psychiatric literature, authors presented the etiological model of mental disorders secondary to the diagnosis of infertility [9]. At the same time the authors drew attention to the importance of psychopathological symptoms for the aetiology of this disorder. Holas et al. also appealed to Berg's models, developed in the eighties of the previous century. Berg introduced: 'model of psychogenic infertility' – according to which, mental disorders and stress may condition the infertility and the 'model of the psychological consequences of infertility' where the psychopathological symptoms may be a consequence of chronic diagnosis and treatment of infertility [9, 10]. Currently, long-functioning duality between 'psychogenic infertility' hypothesis and the concept of 'psychological consequences of infertility' has been replaced with bilateral model that links infertility and its psychological and social consequences [11, 12]. Psychogenic hypotheses of infertility were replaced by stress models and models of coping with the experience of infertility [11–13]. In addition,

in recent years the results of several cohort studies on fertility of people with mental disorders were published. Another group of recent research concerned the prevalence of mental disorders among people whose therapy did not lead to the birth of a living child [14–17]. The results of these studies shed new light on aspects of the relationship of fertility and the occurrence of mental disorders.

Method

In the present work we have analyzed the studies available through MEDLINE, concerning the relationship between the infertility therapy and mental disorders and fertility of persons with mental disorders. In our search we used the following keywords: infertility treatment, fertility, mental disorders. In the following analysis we included studies, the results of whose were important from the clinical point of view, and covered sufficiently abundant research groups. A separate analysis of the literature was performed in relation to Polish literature. We analyzed all of the work published until 2014 in periodicals of Polish psychiatric and gynaecological society (i.e. in *Psychiatria Polska* and *Ginekologia Polska*), which focused on the subject of assisted reproduction. In a further analysis we included Polish works, which focused on fertility, infertility diagnosis and treatment of infertility, in the context of the prevalence of mental disorders. In both Polish periodicals we have not found any studies on the fertility of people with mental disorders.

Aim

The aim of this paper was the analysis of the studies concerning the mental health aspects in the course of the infertility treatment in terms of their relevance to clinical practice in the field of psychiatric-psychological support for patients treated for infertility.

Effect of the ineffective infertility treatment on the development of mental disorders

The authors of the aforementioned Polish work examining the relationship between the mental disorders and the infertility stressed the importance of psychological factors, which may constitute a significant part of the infertility problem [9]. In contrast, the concerns of the authors of that work were related to the severity of mental dysfunctions that may be treated as a “normal emotional reaction” to the diagnosis and the treatment of infertility [9].

The results of the research concerning the ineffective infertility therapy and the risk of mental disorders are inconclusive. In a small study of Lund et al. it was demonstrated that as many as 15% of women and 6% of men whose infertility therapy did not end with the birth of a living child suffered from the symptoms of severe depression [18]. Williams et al. on the basis of a critical analysis of the literature concluded

that ineffective treatment for infertility is a factor of the increased risk of depressive symptoms that could lead to the development of major depression [19].

The largest published studies in this area is the work of Baldur-Felskov, wherein the data on 98,320 Danish women were analyzed, and Yli-Kuha work based on an analysis of Finnish population ($n = 9,175$) [15, 16]. Both studies have produced conflicting results. Baldur-Felskov work revealed that previous unsuccessful treatment for infertility increases the risk of psychiatric hospitalization, and Yli-Kuha's work – that it decreases the risk of psychiatric hospitalization [15, 16]. A retrospective Danish cohort study was designed using data from Danish women evaluated for fertility problems during 1973–2008; it revealed that women diagnosed with infertility, who did not succeed giving birth had the higher hospitalization rate due to psychiatric reasons, compared with women who, despite the initial diagnosis of infertility, gave birth [15]. The most common cause of psychiatric hospitalization in this group were mental disorders associated with the use of alcohol and psychoactive substances and psychotic disorders (including schizophrenia) [15]. In contrast, previous unsuccessful treatment for infertility did not affect the risk of hospitalization for the diagnosis of eating disorders, anxiety disorders and obsessive-compulsive disorder [15]. For the diagnosis of affective disorder previous unsuccessful treatment for infertility even reduced the risk of psychiatric hospitalization [15]. Based on the results of this study, it is not known, however, whether early reproductive failure actually did not change the risk of developing psychiatric disorders from category of adjustment, anxiety, affective and eating disorders. This is due to the fact that no data were analyzed concerning the outpatient psychiatric treatment of women previously diagnosed with infertility. Aforementioned categories of disorders are frequently the subject of outpatient therapy and they do not require psychiatric hospitalization as often as psychotic disorder or intoxication with alcohol or psychoactive substances [15]. In addition, the results of cohort studies registration can also be affected by the fact that women with infertility and concomitant severe mental disorders may be disqualified from ART treatment due to contraindications to the use of hormone therapy. This can reduce the number of women with severe mental illness in the records of patients treated with ART.

In another Finnish cohort study conducted in the years 1969–1998 on 9,175 patients previously treated for infertility, psychiatric hospitalization rate was analyzed. It has been demonstrated that women diagnosed with infertility were rarely hospitalized for psychiatric reasons due to affective, anxiety, personality and eating disorders as well as substance abuse and psychotic disorders. However, this difference was statistically significant only for psychotic disorders [16].

In another Finnish cohort study of childless people ($n = 2,291$) in the past treated for infertility, it was shown that such patients are at increased risk of developing dysthymia and anxiety disorders compared to women from the control group [20]. For childless men of the study population, the diagnosis of infertility was associated with worse quality of life compared to those with preserved fertility. It did not result in a higher risk of developing mental disorders. While in women who did not give

birth, but were diagnosed and/or treated for infertility in the past there was a higher prevalence of panic disorder compared with the general population [20].

Depression and infertility

Most epidemiological studies report high intensity of anxiety and depression in people who participate in ART. However, due to the large methodological differences between the analyzed studies the results were very different. A number of studies identifies an increased incidence of depressive symptoms in patients treated for infertility [21–24]. Such a conclusion was also confirmed in a critical analysis of previous studies conducted by Williams et al. who found that for women taking the therapy for infertility an increased incidence of depressive symptoms and major depression are observed [19].

Table 1. The main conclusions of the studies on the prevalence of symptoms of depression and anxiety in patients treated for infertility

Study	Study population	Method	Conclusions
Chiba et al. 1997 [22]	Infertile women being treated for infertility; N = 107	State Trait Anxiety Inventory (STAI), Centre for Epidemiologic Studies Depression Scale (CES-D), and Cornell Medical Index (CMI)	Infertile women are considered to become more depressive the longer treatment persists
Beutel et al. 1999 [21]	Cohort of couples undergoing ART women N = 280 men N = 281	Depression Scale (D-S)	Infertile women significantly more depressed than their age-matched female controls from the general population; marginally elevated depression scores in men compared to their controls
Matsubayashi et al. 2001 [24]	Infertile women (N = 101) compared to healthy pregnant women (N = 81)	The hospital anxiety and depression scale (HADS) and the profile of mood states (POMS)	The scores for anxiety, depression, hostility, aggression, anhedonia of infertile women were significantly higher than those of pregnant women. Fatigue scores were higher in pregnant women, compared with infertile women
Chen et al. 2004 [23]	Consecutive women visiting the assisted reproduction clinic (N = 112)	Diagnosis of psychiatric disorders was made using a structured interview, the Mini-International Neuropsychiatric Interview (MINI).	Psychiatric disorders were present in 40.2% of patients; 23.2% – generalized anxiety disorder; 17% – major depressive disorder; dysthymic disorder in 9.8% of patients
Petersen et al. 2014 [14]	Couples undergoing fertility treatments in Denmark in the year 2000 (N = 1,406)	Mental Health Inventory 5 from the Short Form Health Survey 36. Infertility distress was measured by the COMPI Fertility Problem Stress Scales	Severe depressive symptoms were reported in 11.6% of women and 4.3% of men, and were significantly associated with increased infertility-related distress at the individual and partner level.

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Sbaragli et al. 2008 [25]	81 infertile couples recruited from an infertility centre before fertility treatment and 70 fertile control couples	Psychiatric screening evaluation for the presence of DSM-IV Axis I mental disorders	The occurrence of current psychiatric disorders was significantly higher among infertile subjects than among fertile controls, especially for adjustment disorder with mixed anxiety and depressed mood (16% vs. 2%) and for binge eating disorder (8% vs. 0)
Volgsten et al. 2008 [26]	545 couples, attending a fertility clinic in Sweden during a two-year period.	Primary Care Evaluation of Mental Disorders (PRIME-MD), based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)	Any psychiatric diagnosis was present in 30.8% of females and in 10.2% of males. Any mood disorder was present in 26.2% of females and 9.2% of males. Major depression prevalent in 10.9% of females and 5.1% of males. Any anxiety disorder was encountered in 14.8% of females and 4.9% males

In one of the recent studies in this field, in a population of 112 women treated for infertility, mental disorders were diagnosed in 40.2% of patients, major depressive disorder in 17% of the respondents, while dysthymia in 9.8% of patients [23]. While severe depressive symptoms were reported in up to 11% of women and more than 4% of their partners (from the group of 1,406 pairs) involved in the treatment of infertility [14]. Anxiety disorders were found in 12–23% of women treated for infertility [25, 26]. In the study conducted by Chen et al. generalized anxiety disorder was found in 23% of patients [23].

Another line of research concerns the impact of depressive symptoms on the effects of infertility treatments (evaluated as the live birth rate). In two recent meta-analyses of this phenomenon it was shown that the diagnosis of depression does not decrease the chance of conceiving [27, 28]. While some research (including a cohort study on a group of 42,880 Danish women participating in ART cycles) show that the incidence of depression is connected with a lower rate of pregnancies observed among people treated for infertility [26, 29]. The Danish cohort study found that women diagnosed with depression prior to ART, participated in fewer treatment cycles, abandoning treatment before all the possibilities of therapy were exhausted [29]. In this study a lower percentage of pregnancies and live births were observed in the group of women previously diagnosed with depression compared to women without depression.

However, the study by Volgsten et al. revealed that the diagnosis of major depressive disorder prior to infertility treatment is linked with the lowest rate of live births [26]. However, in another study it was shown that in women with higher levels of anxiety (both state and trait anxiety measured with Spielberger questionnaire) assessed prior to ART a lower rate of live births is observed compared to women with lower levels of anxiety [30].

According to Freeman et al. women with a history of major depressive disorder may be hypersensitive to the stress of ART, which, together with exposure to medications used for the induction of the ovulation may lead to an increased risk for recurrence of the depressive disorders [31]. Another important aspect of that issue is the effect of drugs used in the infertility therapy for the depressive and anxiety symptoms. Most of the infertility treatment medications are hormones that affect the different levels of the hypothalamic-pituitary-gonadal axis. Little is known about psychiatric adverse effects of such medications, as in any of the previous studies their influence on the occurrence of mental disorders, as an independent variable was not analyzed. Williams et al. in a critical analysis of the literature draw the conclusion that most of the procedures in the field of assisted reproductive technologies independently affects mood, due to the effects of estrogens and progesterone, which may affect the serotonergic pathways [19]. Certain medications used in the treatment of infertility (or their combination), in some clinical circumstances can have pro-psychotic effect. It was reported, for example, for the frequent combination of clomiphene citrate and bromocriptine used for ovulation induction in the course of hyperprolactinaemia [32].

Prevalence of psychotic disorders among persons treated for infertility and fertility of people with mental disorders

Still little is known about the prevalence of psychotic disorders among women treated for infertility. It was observed, however, that fertility rates of patients with schizophrenia are the lowest in comparison with the fertility rates of patients suffering from other mental disorders [33]. It has long been known that the fertility of people with psychosis is lower than in the general population, but it is not clear whether it is due to biological or social reasons [34]

Several studies have confirmed reduced fertility and fecundity rates in patients with psychotic disorders [33–37]. However, for patients with bipolar disorder the fertility rate were comparable to those of healthy control subjects [38].

Table 2. The results of studies on fertility (the ability to have a child) and fecundity (number of children) of people diagnosed with psychotic disorders

Study	Patient (age/gender/diagnosis)	Results
McGrath et al. 1999 [35]	Patients with a diagnosis of psychosis or bipolar disorder from two Australian community hospitals, N = 819	36% of all patients were parents. 595 women with psychoses were mothers. Higher levels of fertility were associated with a later age at first diagnosis

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Haukka et al. 2003 [36]	N = 870,093, All individuals born in Finland from 1950 to 1959,	1.3% were patients with schizophrenia, and 2.8% were their siblings. The mean number of offspring among female siblings was slightly but significantly higher than among women in the general population (1.89 versus 1.83), while the opposite was true for the male siblings (1.57 versus 1.65 among men in the general population). The mean number of offspring among patients with schizophrenia was 0.83 for women and 0.44 for men
Bhatia et al. 2004 [37]	Individuals with schizophrenia or schizoaffective disorder (New Delhi group N = 224, USA Group N = 144)	In the USA sample, male cases were significantly more likely to be single and childless compared with female cases. In contrast, there were no significant gender differences in the Indian sample with regard to the reproductive indices. Men were more frequently single and childless than women
MacCabe et al. 2009 [38]	Swedish birth cohort of individuals born in 1915–1929; N = 12,168	Patients with schizophrenia had fewer children grandchildren than the general population. Patients with affective psychosis did not differ from the general population on any fertility measure
Laursen & Munk-Olsen 2010 [33]	Entire Danish population born after 1950	Compared with the general population, the lowest first-child fertility rate was found among men (IRR = 0.10) and women (IRR = 0.18) with schizophrenia. Bipolar male patients had an IRR = 0.32 and female patients an IRR = 0.36, while male unipolar patients had an IRR = 0.46 and female patients an IRR = 0.57. Conclusions: persons with more severe disorders are less likely to become parents. The longer the time since onset of psychosis, the higher the fertility.
Power et al. 2013 [40]	Patients with the diagnosis of schizophrenia, autism, bipolar disorder, recurrent depression, anorexia nervosa and substance abuse among Swedish population of people born in 1950–1970, i.e. 2.3 million of individuals	The fecundity of patients with schizophrenia, autism, bipolar disorder, anorexia nervosa, or substance abuse was reduced compared with the general population. Reduced fecundity consistently greater among men than women. In the case of diagnosis of depression, fecundity was comparable to general population.
Zimbron et al. 2014 [34]	AESOP study, 515 people with a first psychotic episode (FEP) and 383 controls.	Persons with FEP showed a reduced fertility rate. Women had a greater reduction in fertility rates than. FEP who had previously experienced a stable relationship had an MNC that was comparable to that of the general population and had a later onset of illness. Conclusions: fertility is affected, even prior to the onset of a psychotic illness – influence of biological and social factors

Laursen and Munk-Olsen analyzing data on fertility patterns of patients with mental disorders in the Danish population beginning from 1950, noted the lowest fertility rate for men with schizophrenia. Then, higher fertility rate was observed in women

with schizophrenia, women with bipolar disorder, in men with bipolar disorder and in men with unipolar depression and in women with unipolar depression [33]. Laursen and Munk-Olsen concluded that the more severe was mental disorders observed in the subjects, the lower was their fertility rate. In contrast, the more time elapsed since diagnosis, the higher was the fertility rate of respondents [33]. In this study, a higher abortion rate in women with severe mental illness was observed, compared to the control group [33]. The authors of the study citing the work of Viguera et al. explained the higher rate of abortion among women with severe mental disorders with the fact of counselling of avoiding of the motherhood [39]. However, even taking into account the higher abortion rate in the analysis it could not explain the reduced fertility rate in subjects with schizophrenia [33].

However, in the Swedish study, which examined the fertility of patients with schizophrenia, bipolar disorder, recurrent depression, anorexia nervosa and addiction, it has been shown that patients with these disorders (except depression) had fertility rates lower than general population [40]. In addition, it was observed that men were characterized by lower fertility compared to women. Only for patients with a diagnosis of depression, fertility rates followed a similar pattern as in the general population.

In another Danish study conducted on a cohort of 42,915 women participating in the ART from 1994 to 2009 demonstrated that 0.6% of them were diagnosed with psychosis before, during or after their infertility treatment [41]. From the group of all psychotic women from that cohort 53% received a diagnosis of psychotic disorder before, 2.7% during and 41% after ART treatment. For women who were diagnosed with psychosis before proceeding to ART, the mean time from psychotic episode, and starting the ART therapy was 5–7 years, and the most common diagnosis in this group were acute and transient psychotic disorders. In addition, this study showed that the prevalence of women with a psychotic diagnosis in fertility treatment was lower than the prevalence in the general population [41].

In Finish cohort study it was revealed that in the population of infertile women being treated for infertility the incidence of hospitalization for both addiction, affective, anxiety, personality, eating and psychotic disorders is lower than in the general population [16]. Based on the results of work by Yli-Kuha et al. the incidence of hospitalization for psychotic disorders in a population of infertile women lower than in the general population, can be inferred [16]. However, on the basis of this work it is not possible to estimate the prevalence of untreated psychiatric psychotic symptoms, or the frequency of the antipsychotic treatment on an outpatients basis. It is therefore difficult to generalize the results of this study on the whole population of infertile people. In addition, it is likely that patients treated for infertility could avoid disclosing mental disorders or psychiatric treatment (especially pharmacotherapy), due to concerns about the risks of interference psychopharmacologic treatment and infertility therapy. The use of psychiatric medication itself could be interpreted by doctors providing qualifications for ART as contraindication for participation in the further treatment.

Determinants of anorexia nervosa among persons treated for infertility

In studies conducted in small research groups it was shown that the risk of eating disorders is higher among women with a diagnosis of infertility than in general population [25, 42]. However, in the already mentioned study of Baldur-Felskov et al., it was demonstrated that earlier infertility diagnosis and/or subsequent ineffective infertility therapy are not associated with an increased risk for eating disorders [15].

Early studies on the relationship between eating disorders, and infertility showed that fertility of women diagnosed with anorexia nervosa (AN) is reduced comparing to the normal population [17]. In recent years, a cohort study of the entire Swedish population (i.e. 2.3 million people born between 1950 and 1970), confirmed that the fertility of people with anorexia nervosa is reduced compared to the general population [40]. It was the largest study conducted to date in this field.

In the past, the phenomenon of reduced fertility in eating disorders was related to secondary amenorrhea (amenorrhea secundaria) occurring in 68–89% in women with diagnosis of anorexia nervosa [17]. In addition, a reduced fertility has long been associated with the psychological aspects of AN [17]. It was assumed that the occurrence of eating disorders leads to dysregulation of the hypothalamic-pituitary-gonadal axis and consequently to the irregularities in the pulsatile secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). This was combined with the long-term effect of reduced fertility in these patients [43].

However, according to experts of the European Society of Human Reproduction and Embryology (ESHRE), even a small change in eating habits can lead to fertility improvement. This is due to the fact that it is energy balance, and not the nutritional status and the body fat amount is directly related to the functioning of the hypothalamic-pituitary-gonadal axis and subsequently to fertility status. The proper function of this axis can be restored even with a slight increase of daily energy balance [44].

In a cohort study of Bulik et al. conducted using registry data of Norwegian women of the epidemiological program “Mother and Child” the conclusions of ESHRE consensus was confirmed [17, 44]. Among 62,060 women who had children, 62 women with a diagnosis of anorexia nervosa (AN) were identified. It has been shown that women diagnosed with AN more often reported that their pregnancies were not planned compared to women from the control group (i.e. at a frequency of 50% for women with AN, compared to 18.9% for healthy women). Whereas the rate of abortions was also higher in women with AN (amounting to 24.2%) compared to 14.6% of women without a diagnosis of mental disorders [17]. The authors of the study noted that both secondary amenorrhea (amenorrhea secundaria), and irregular menstrual cycles (dysmenorrhea) may lead to false conclusions concerning the reduction of fertility in the course of eating disorders. This may result in an increased percentage of unplanned pregnancies and consequently increased percentage of abortions performed by women diagnosed with AN [17]. In pregnant women with eating disorders there is an increased risk of complications of pregnancy and childbirth (i.e. miscarriage, intrauterine growth

retardation or premature birth) [45]. Therefore, according to some authors the screening for the presence of eating disorders should be included in the routine diagnostics of pregnant women [42].

Does a specific personality profile of persons with a diagnosis of infertility exist?

In the few works the personality profile of the women experiencing the infertility was analyzed. However, these studies were conducted on very small research groups, whose results cannot be compared due to methodological differences related to methods used for the diagnosis of personality. In the study of Csemiczky et al. comparing 22 women with a diagnosis of tubal infertility with fertile controls showed that women entering the ART are characterized by a higher level of suspicion, guilt and hostility, but a lower severity of somatic symptoms of anxiety measured with the use of Karolinska Scales of Personality [30]. Conclusions from the study of Noorbala et al. suggest that women treated for infertility compared to controls have elevated levels of psychoticism and interpersonal sensitivity as well as depression and anxiety measured using a psychopathological symptoms questionnaire SCL-90-R [46]. However, in the study of Marci et al. no differences in personality profile questionnaire assessed using ACL (Adjective Check List) of patients with infertility were observed [13]. No differences were observed for both subgroups i.e. in couples who just received a diagnosis of infertility and in those who have already participated in ART procedures, compared to the control group [12].

The impact of psychiatric treatment on the effectiveness of the infertility therapy

In many therapeutic models applicable to persons with infertility the importance of mental well-being and low levels of depression and anxiety for improving the effectiveness of infertility therapy are emphasized. However, little controlled methodologically correct studies were carried out in this field. Therapeutic standards of psychiatric help for people being treated for infertility, and experiencing symptoms of mental deterioration in the course of ART procedures were not developed so far. An additional factor impeding the psychiatric treatment of such persons could be their aversion to the pharmacological psychiatric treatment resulting from concerns about teratogenicity of psychoactive medications in case possible conception. The study, which compared the effect of depressed mood stabilization before infertility treatment on the effect of infertility therapy has confirmed that psychiatric help was a factor that multiplied the percentage of obtained pregnancies [47]. In a randomized study on the effect of psychotherapeutic and psychopharmacological interventions on the effects of infertility treatment among 140 couples experiencing symptoms of mild or moderate depression during ART procedures it was revealed that among couples who received such interventions the reported number of pregnancies was fourteen times higher than in couples from a control group [47]. Intervention used in this study consisted of 6 to 8

sessions of individual psychotherapy combined with pharmacotherapy with fluoxetine (20–60mg per day) [47]. On the basis on the results of this study the authors proposed the inclusion of diagnostic psychiatric counselling for all women entering the ART procedures in order to identify the psychopathological symptoms and implement treatment for women suffering from mental disorders.

In the retrospective analysis of the effects of antidepressants on the success of ART therapy showed no significant differences concerning the response to the induction of the ovulation, the number of retrieved oocytes and the amount and maturity of obtained embryos. However, the final number of confirmed pregnancies was slightly lower among women who were treated with SSRIs, compared to women treated with antidepressants (40% vs. 51%) [48]. Additionally, in a meta-analysis of cohort studies evaluating the effects of antidepressants on the early spontaneous miscarriage rate it has been shown that for women treated with antidepressants the percentage of miscarriages was slightly higher than for the untreated women. None of the groups of drugs was safer in this respect than the other [49].

While, in the study of Domar et al. the effects of the group cognitive-behavioural therapy compared to standard supportive therapy and lack of treatment were evaluated on the percentage of pregnancies obtained in the group of one hundred and eighty patients. The subjects were diagnosed with infertility during the preceding two years [50]. A significantly higher proportion of confirmed pregnancies were reported in both subgroups of patients that received ten sessions of group cognitive-behavioural therapy or supportive therapy. Similar beneficial effect of a structured program consisted of five sessions of group therapy on the confirmed pregnancies rate were observed in a controlled study of Hosaka et al. [51].

Table 3. The results of studies concerning the impact of psychotherapeutic and/or pharmacotherapeutic interventions for the results of infertility treatment in people participating in ART procedures

Study	Study group	Type of intervention	Results
Domar et al. 2000 [50]	N = 184 women who had been trying to get pregnant for 12 to 24 months	10 weeks of cognitive-behavioural therapy (N = 47), support group (N = 48), treatment as usual group (N = 25)	Increased pregnancy rates in both group receiving both types of psychotherapy
Hosaka et al. 2002 [51]	Infertile women, N = 74	Group receiving 5-session intervention program (N = 37), treatment as usual group (N = 37)	The pregnancy rate in the intervention group was significantly higher than that of controls (37.8% vs. 13.5%, p = 0.03)

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Klock et al. 2004 [48]	Women taking SSRI in the course of in-vitro fertilisation (N = 40) compared with a matched comparison group (N = 51)	A retrospective chart review study of women taking selective serotonin reuptake inhibitors antidepressants compared with a matched comparison group	50% of women taking selective serotonin reuptake inhibitors were pregnant compared to 41% of women not taking selective serotonin reuptake inhibitors No differences in obtained oocytes, the quantity of the eight cell embryos and initial values of beta-hCG
Ramzenzadeh et al. 2011 [47]	140 couples (N = 280) with depression (from mild to severe) in at least one of the spouses	6-8 sessions of psychotherapy (individually) before beginning infertility treatment and fluoxetine at 20–60 mg per day during the psychotherapy period comparing with treatment as usual	Pregnancy occurred in 33 (47.1%) couples in the treatment group and in only 5 (7.1%) couples in the control group

Discussion

Today, infertility is an increasingly common medical and social problem. A number of performed ART cycles is increasing every year. Most research indicates that the presence of psychiatric disorders (including depressive disorders, the most common among them) in patients treated for infertility, can affect the efficacy of gynaecological procedures. Some research also indicates that an ineffective treatment for infertility (which has not led to the birth of a living child), is an independent risk factor for mental disorders (especially psychotic disorders and addiction) [15]. In recent years, the results of several cohort studies concerning the relationship between infertility therapy and the risk of psychiatric hospitalization were published. Unfortunately the results of these studies are inconclusive. For example, the study of Finnish population revealed that women treated for infertility are less frequently hospitalized for psychiatric reason than those of the control population [16]. While the study of Danish population revealed that these patients are more frequently hospitalized for psychiatric reasons, especially due to psychotic disorders and substance abuse [15]. Another important issue seems to be the research results concerning the patterns of fertility in the course of the different categories of mental disorders. These studies demonstrated that in the course of affective disorders, psychotic disorders and anorexia nervosa the fertility is decreased [33, 40]. The reduced fertility is related to the severity and category of mental disorder [33].

The therapy of mental disorders in the course of infertility treatment is combined with a number of different clinical issues, for which only marginal attention has been paid in the literature so far. One of them represents the assessment of the risk of relapse

of mental disorders in the course of infertility treatment considered as a long-term stress factor. Equally important but poorly recognized seems to be the psychiatric evaluation of possible adverse effects of drugs used in the course of infertility treatment (including the hormones acting on different levels of the hypothalamic-pituitary-gonadal axis, most commonly used for this indication). Standards for psychiatric evaluation of persons entering the ART, for psychiatric considerations during the successive ART cycles and for psychiatric treatment of mental disorder after the unsuccessful infertility treatment (which did not lead to the birth of a living child) have not been developed yet. A number of data has been accumulated concerning the adverse effects of the symptoms (mainly depression and anxiety) and/or the mental disorders on the results of infertility treatment. Unfortunately it was not reflected in the development of standards of psychiatric considerations associated with the presence of psychiatric disorders in the course of ART. These considerations would cover the mental state stabilization in order to improve the effectiveness of gynaecological treatment. Many authors suggest the introduction of an interdisciplinary therapeutic team for women treated for infertility – taking into account the participation of a psychiatrist and a psychologist.

According to ESHRE data in large centres where treatment of infertility was supported by mental health teams for many years its central task consisted of the support for couples going through a crisis of infertility diagnosis [52]. In recent years, psychological counselling tailored for specific problems such as coping with two-week period before pregnancy test, helping men for semen analysis or supporting the decisions regarding the use of gametes donation or surrogate mothers. Another important subgroup who require increased attention from psychiatrists is a subgroup of women who have experienced psychiatric symptoms before the infertility treatment and those women for whom the infertility treatment caused a significant deterioration of their mental status. Increased attention from psychiatrists is also required for patients whose gynaecological treatment has not led to a live birth. A majority of the research on such patients stressed the increased risk of severe psychiatric disorders (particularly psychotic disorders and addiction) in the course of failure of infertility treatment [15]. In contrast, at the end of infertility treatment without getting pregnant, this sub-group ceases to receive an institutional medical help (at infertility clinics) but still need psychological and psychiatric help.

Conclusions

1. In patients treated for infertility mental disorders represent very common clinical problem. Depressive disorders and anxiety disorders are the most frequently observed among them.
2. Ineffective treatment for infertility constitutes an independent risk factor for development of mental disorders, particularly psychotic disorders and substance abuse.

3. Despite the increasing prevalence of ART procedures, there are no uniform standards for psychological and psychiatric support concerning the infertility treatment and mental health complications of diagnosis and treatment of infertility.

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